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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/524,638

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Dieter Flockerzi

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NATH & ASSOCIATES PLLC
112 South West Street
Alexandria, VA 22314

EXAMINER

DESAI, RITA J

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

10/05/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/524,638

Applicant(s)

FLOCKERZI, DIETER

Examiner

Rita J. Desai

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11, 13, 15-17 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/28/2000</u> . | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 1-11, 13, 14-17.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1- 11, 13, 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds wherein R2 and R3 do not form a ring , R4 is a H, R6-R16 are either a H or an alkyl or a cycloalkyl or combine to form a ring such as a pyrrolidine, morpholine, azepine , piperazine , piperidinyl does not reasonably provide enablement for

- 1) all the other various substitutents for the various R's.
- 2) solvates,, hydrate or hydrate of a salt or solvate of a salt or tautomers.
- 3) with respect to claims 13, 15-17, method of treating an illness treatable by a PDE4 inhibitor , an airway "disorder" nor "dermatoses."

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and

Art Unit: 1625

whether any necessary experimentation is “undue”. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims: The instant claims encompass many compounds with numerous groups substituted on it.

2) The nature of the invention: The invention is a chemical compound used as a pharmaceutical.

3) The state of the prior art: The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Art Unit: 1625

Also the state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of diseases as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

4) The level of one of ordinary skill: The ordinary artisan is highly skilled.

5) The level of predictability in the art:

How to use:- It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts

Art Unit: 1625

cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain)).

How to make :-

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis

Art Unit: 1625

usually implies will be able to appraise such workChemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) " Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Thus it is not very easy to synthesis compounds.

6) The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. There is some PDE3 and PDE4 activity data however it does not teach that it can treat any PDE related disease, or any airway disorder or dermatosa. This does not in any way indicate that the full scope of the compounds can treat all the various diseases as claimed..

There are no compounds wherein R2 and R3 form a dioxo ring. It changes the core of the compounds.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here. As per MPEP 2164.01 (b):

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the

Art Unit: 1625

apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

There are no starting material provided with respect to the R5 being all the various groups.

Regarding solvates and hydrates :- The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

7) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of all the above factors, guidance and state of the art , it would require an undue amount of experimentation to make the invention of the claims with various substitutents , or for using them to treat the diseases ie. Pharmaceutical compositions also..

Art Unit: 1625

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1625

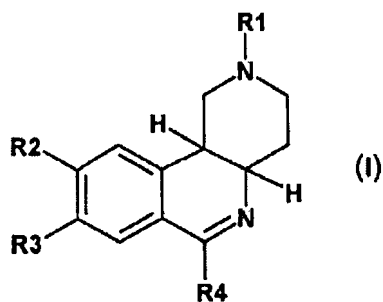
having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11, 13, 15-17 are rejected under 35 U.S.C. 103(a) as being obvious over WO 98/21208 Gutterer et al (US 6008215) also WO 98/40382

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The prior art teaches similar compounds with the same core.

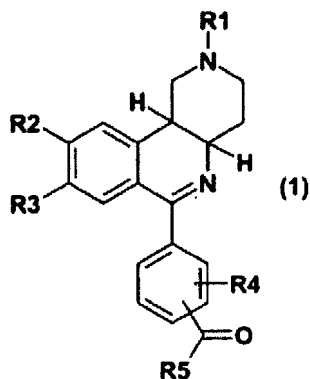
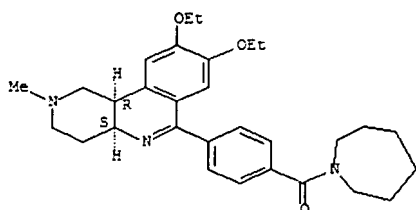
Art Unit: 1625



wherein R4 is a phenyl

substituted by CO-R7, C0R8 , with R8 being NR81R82 and they forming a ring.

One of the species amongst other (piperidine, morpholine etc) is given by the following.



Applicants compounds are , which

with R5

being a N containing radical.

Art Unit: 1625

US 6306869 and 6143759 Flockeral et al also teach compounds with the same core only difference being the substituents on the R4 phenyl ring.

The use / utility is the same for all the compounds. the only difference is the R5 group of the applicants.

Since the prior art compounds are so closely related and the only difference is the substituent on the phenyl, one of skilled in the art would have been motivated to try out other groups at the same position and have a reasonable expectation of success at obtaining compounds with the same activity.

Thus the compounds are prima-facie obvious over those of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Art Unit: 1625

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13, 15-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1-13 of U.S. Patent No. 6008215,

claims 1-10 of US 6306869 and

claims 1-12 of US 6143759

in view of each other. Please see the 103 rejection *supra*.

Claims 1-11, 13, 15-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6936622. Although the conflicting claims are not identical, they are not patentably distinct from each other because They are drawn to the same R5 substituents and they have the same utility. See claim 1.

Art Unit: 1625

21

macol 1991: 344, 682-690] using cAMP as substrate. The PDE3 inhibitor metapizone (1 μ M) was used to suppress the PDE3 activity emanating from contaminated platelets.

The IC_{50} values were determined from the concentration-inhibition curves by nonlinear regression.

B. Results

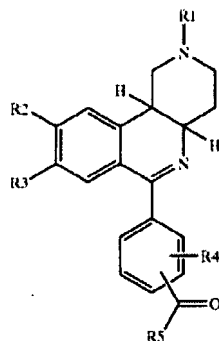
In table 1 below, the inhibitory concentrations according to section A1 [inhibitory concentrations as $-\log IC_{50}$ (mol/l)] are indicated for a number of compounds according to the invention for the PDE4 and the PDE3 isoenzyme. The number of the compounds corresponds to the numbers of the examples in the section End products.

TABLE 1

Compound	PDE4 [$-\log IC_{50}$ mol/l]	PDE3 [$-\log IC_{50}$ mol/l]
1	9.22	6.87
2	9.77	7.37
3	9.39	7.06
4	8.34	5.94
5	9.01	6.89
6	9.13	6.44
7	8.83	6.71
10	8.15	6.05
11	8.41	6.26
13	9.34	7.04
14	8.82	6.51
15	9.11	6.81
16	9.65	6.78
17	9.34	6.91
18	8.76	6.61
19	9.50	6.88
20	9.65	7.01
21	9.40	6.89
22	7.71	6.17

What is claimed is:

1. A compound of the formula I,



in which

R1 is 1-4C-alkyl,

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R3 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

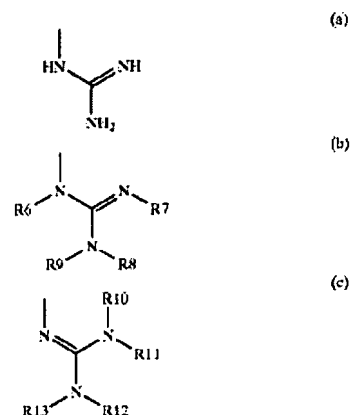
or in which

R2 and R3 together are a 1-20-alkylenedioxy group,

R4 is hydrogen, halogen, nitro, 1-4C-alkyl, trifluoromethyl or 1-4C-alkoxy.

22

R5 is a radical of the formula (a), (b) or (c)



in which

if R5 is a radical of the formula (b), either

R6, R7, R8 and R9 independently of one another are hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7-cycloalkylmethyl or hydroxy-2-4-C-alkyl, or

R6 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7-cycloalkylmethyl or hydroxy-2-4-C-alkyl,

R7 is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7-cycloalkylmethyl or hydroxy-2-4-C-alkyl,

R8 and R9, together and including the nitrogen atom to which both are bonded, are a 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl or 4-(1-4C-alkyl)-piperazin-1-yl radical,

in which

if R5 is a radical of the formula (c), either

R10, R11, R12 and R13 independently of one another are hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7-cycloalkylmethyl or hydroxy-2-4-C-alkyl, or

R10 and R11 independently of one another are hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7-cycloalkylmethyl or hydroxy-2-4-C-alkyl, and

R12 and R13, together and including the nitrogen atom to which both are bonded, are a 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl or 4-(1-4C-alkyl)-piperazin-1-yl radical, or

R10 and R11, together and including the nitrogen atom to which both are bonded, are a 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl or 4-(1-4C-alkyl)-piperazin-1-yl radical, and

R12 and R13, together and including the nitrogen atom to which both are bonded, are a 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl or 4-(1-4C-alkyl)-piperazin-1-yl radical, or

R10 and R13 independently of one another are hydrogen or 1-4C-alkyl, and

R and R12, together and including the N—C(=N)—N structure to which they are bonded, are a hexahydropyrimidin-2-ylidene or imidazolidin-2-ylidene radical,

or a salt, solvate, hydrate, solvate of a salt, hydrate of a salt, N-oxide, enantiomer, E/Z isomer or tautomer thereof, or a salt of an N-oxide, enantiomer, E/Z isomer or tautomer thereof.

2. A compound of the formula I as claimed in claim 1, in which

Conclusion

Claims 1-11, 13, 15-17 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625

R. Desai
9/26/07

R.D.
September 26, 2007